Ethnic Difference in Hematological Toxicity in Patients with Non-small Cell Lung Cancer Treated with Chemotherapy

A Pooled Analysis on Asian versus Non-Asian in Phase II and III Clinical Trials

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Introduction: There are a large number of global clinical trials ongoing for patients with non-small cell lung cancer (NSCLC). Ethnic difference in toxicity has not been adequately studied.

Methods: We performed a systematic search in PubMed for randomized phase II and III trials of NSCLC from January 2000 to December 2009, examining ethnic difference in hematological toxicity due to cytotoxic chemotherapy. Ethnicity was classified into Asian and non-Asian. We chose three treatment regimens used for NSCLC globally: cisplatin plus gemcitabine (CG), cisplatin plus vinorelbine (CV), and carboplatin plus paclitaxel (CP). We applied sensitivity analysis to examine unreported ethnic differences in hematological toxicities by changing the percentage of Asian patients from 0 to 18% in trials reported from the United States and Europe.

Results: We identified 12 phase II trials and 38 phase III trials of NSCLC with a total of 11,271 patients. Among these, 14 trials had reported ethnic origins. Grade 3/4 toxicities were more frequently observed in the Asian studies. On the basis of sensitivity analysis, odds ratio of grade 3/4 neutropenia was significantly higher in Asian patients than non-Asian, when treated with CG (OR = 1.55–3.45, $p < 0.001$), CV (OR = 2.99–4.43, $p < 0.001$), and CP (OR = 4.79–6.22, $p < 0.001$). Grade 3/4 anemia was also significantly higher in Asians with CG (OR = 3.10–3.27, $p < 0.001$), CV (OR = 1.99–2.43, $p < 0.001$), and CP (OR = 1.34–1.52, $p < 0.001$–0.004). However, no significant difference was observed in thrombocytopenia with CG (OR = 0.66–2.04, $p < 0.001$–1.000), CV (OR = 0.42–0.57, $p = 0.097$–0.323), or CP (OR = 1.21–1.39, $p = 0.114$–0.152).

Conclusions: Severe hematological toxicity was frequently observed in Asian patients compared with non-Asian (mostly whites) in the treatment of chemotherapy for NSCLC.

Key Words: Non-small cell lung cancer, Chemotherapy, Ethnic difference, Sensitivity analysis.

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A growing number of global clinical trials are ongoing for patients with non-small cell lung cancer (NSCLC), which will likely be further enhanced by the recent emergence of molecular targeting agents. Differences in toxicity because of several chemotherapeutic agents for lung cancer among different ethnicity have been reported.[1,2] Epidermal growth factor receptor (EGFR)-targeting agents are the first molecular targeting agents on which ethnic differences have been intensively discussed between white and Asian patients.[3,4]

Ethnic difference in clinical benefit from EGFR tyrosine kinase inhibitors (TKIs) treatment has been emphasized, whereas the side effects caused by cytotoxic chemotherapy have not been fully studied. There is some evidence for ethnic differences in the pharmacokinetics and in toxicity from anticancer drugs, in particular between Asian and white patients. It has been reported that allelic variants of genes encoding drug-metabolizing enzymes are expressed with different incidences in different ethnic groups.[5]

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For example, irinotecan is a cytotoxic drug for treatment of small cell lung cancer and NSCLC, and association between the toxicity and single-nucleotide polymorphism has been studied intensively about uridine diphosphate glucuronosyltransferase 1A1-glucuronosyltransferase 1A1. In fact, in comparative outcomes analysis of Japan Clinical Oncology Group 9511 and Southwest Oncology Group (SWOG) 0124 in extensive stage small cell lung cancer, significant differences in toxicity were observed in cisplatin plus irinotecan between the two populations.[6] Grade 3 or higher neutropenia was observed in 65% of Japanese patients, while 34% in the United States. It is suggested that carefully planned global clinical trials are vital to elucidate potential ethnic differences in adverse effects.

In this study, we report an ethnic difference in toxicity due to chemotherapy for patients with NSCLC through systematic review of the literature. Platinum-containing chemotherapy is still the cornerstone of treatment for patients,[7] and we chose treatment regimens that were globally used, including cisplatin plus gemcitabine (CG), cisplatin plus vinorelbine (CV), and carboplatin plus paclitaxel (CP) in NSCLC. The target ethnicity in this study was Asians and non-Asians who were mainly white.

METHODS

Literature Search and Data Extraction

Randomized trials with chemotherapy regimens of CP, CG, and CV in NSCLC published from January 1, 2000, to December 31, 2009, were identified from MEDLINE. We used keywords "nonsmall cell lung cancer," "cisplatin," "gemcitabine," "vinorelbine," "carboplatin," "paclitaxel," "phase II," "phase III," and "randomized trial." The trials with number of patients less than 50 were excluded to better ensure reliability. Search results were limited to reports written in the English language.

To evaluate the toxicity of chemotherapy, we excluded reports of postoperative chemotherapy, preoperative chemotherapy, and chemotherapy for elderly or poor performance status and chose the reports that used chemotherapy agents with doses and schedules close to those in Japan. We adopted the trials with cisplatin 75 to 80 mg/m^2 and gemcitabine 1000 to 1250 mg/m^2, every 3 weeks, and the trials with cisplatin 75 to 80 mg/m^2 and vinorelbine 25 to 30 mg/m^2. Similarly, we adopted the trials with carboplatin area under the curve 5 to 6 mg/ml/min and paclitaxel 200 to 225 mg/m^2. Trials involving radiation therapy were excluded. For each trial, data on sample size, characteristics of ethnicity, toxicity of neutropenia, anemia, and thrombocytopenia were collected. Each study has its own measure to evaluate side effects, which were World Health Organization criteria and the National Cancer Institute's common toxicity criteria version 1 to 4. Although there is a slight difference among them, the boundary of grades 2 and 3 is the same.

Literature search was performed independently by two investigators (Y.H. and T.T.) to assess the reliability of data extraction.

Statistical Analysis

To evaluate ethnic difference in toxicity due to chemotherapies, we calculated actual number of patients from published data.

Sample distributions for the patients with and without toxicities were tested with the χ^2 test and odds ratio (OR) with its 95% confidence interval. Because a certain number of reports did not include ethnicity information, we were uncertain of the ratio of Asian patients in study population in each clinical trial. We were also uncertain of the occurrence of

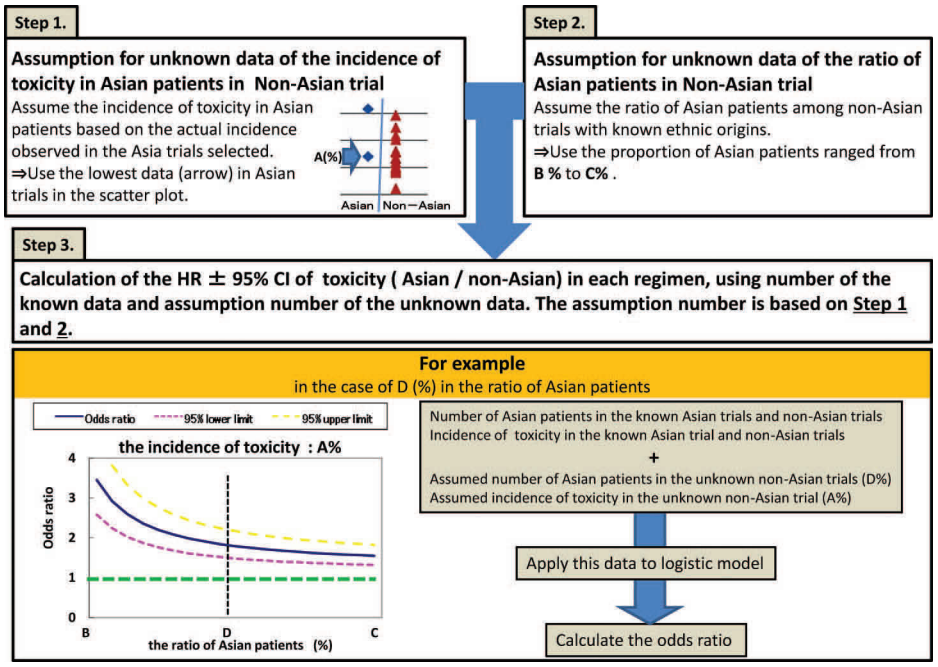
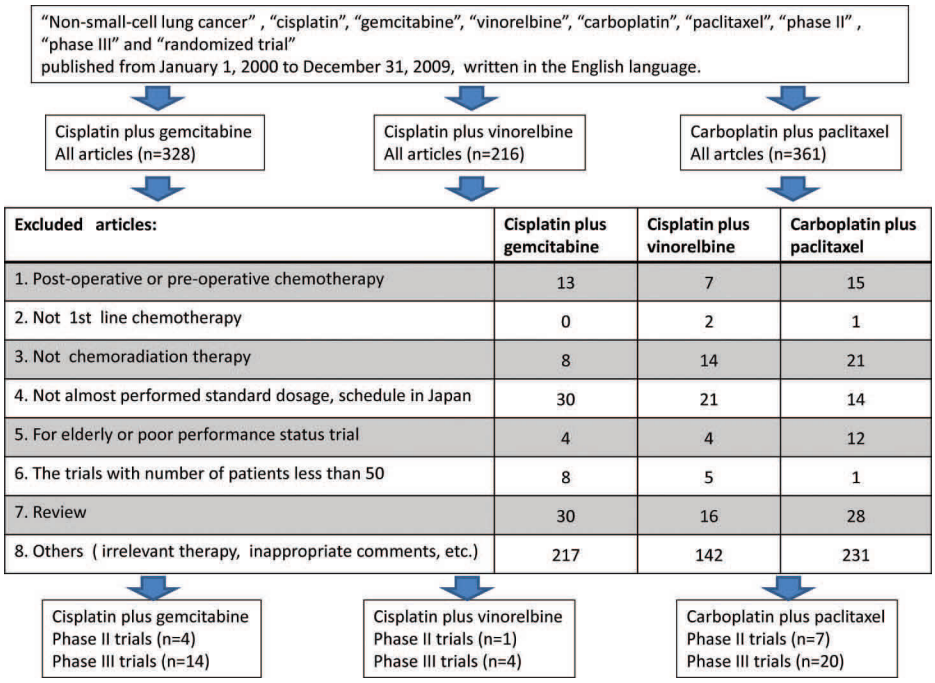


FIGURE 1. Schematic diagram of sensitivity analysis.



Excluded articles:	Cisplatin plus gemcitabine	Cisplatin plus vinorelbine	Carboplatin plus paclitaxel
1. Post-operative or pre-operative chemotherapy	13	7	15
2. Not 1st line chemotherapy	0	2	1
3. Not chemoradiation therapy	8	14	21
4. Not almost performed standard dosage, schedule in Japan	30	21	14
5. For elderly or poor performance status trial	4	4	12
6. The trials with number of patients less than 50	8	5	1
7. Review	30	16	28
8. Others (irrelevant therapy, inappropriate comments, etc.)	217	142	231

FIGURE 2. Flow chart showing the progress of trials through the review.

toxicity in the Asian patients. As shown in Figure 1, we used sensitivity analysis by systematically repeating the statistical analysis using different assumptions for the ratio of Asian patients in clinical trials performed in the United States and Europe. Sensitivity analysis can be used to determine how different values of an independent variable will impact a particular dependent variable under a given set of assumptions when the study involves uncertainty in data distributions.[8] Ratio of ethnicity is determined based on the trials that include ethnicity information. We applied the ranged ratios of Asian patients to the trials in which the racial ratio was not described. We assumed the incidence of hematological toxicity in Asian patients based on the actual incidence observed in the trials selected.

As for survival, we examined whether there are any differences in the distribution of median overall survival between Asian and US/Europe trials using Student's t test.

A p value less than 0.05 was considered statistically significant, and all reported p values were obtained with two-sided manner. All statistical analyses were performed using SPSS 16.0 for Windows (SPSS, Inc, Chicago, IL).

RESULTS

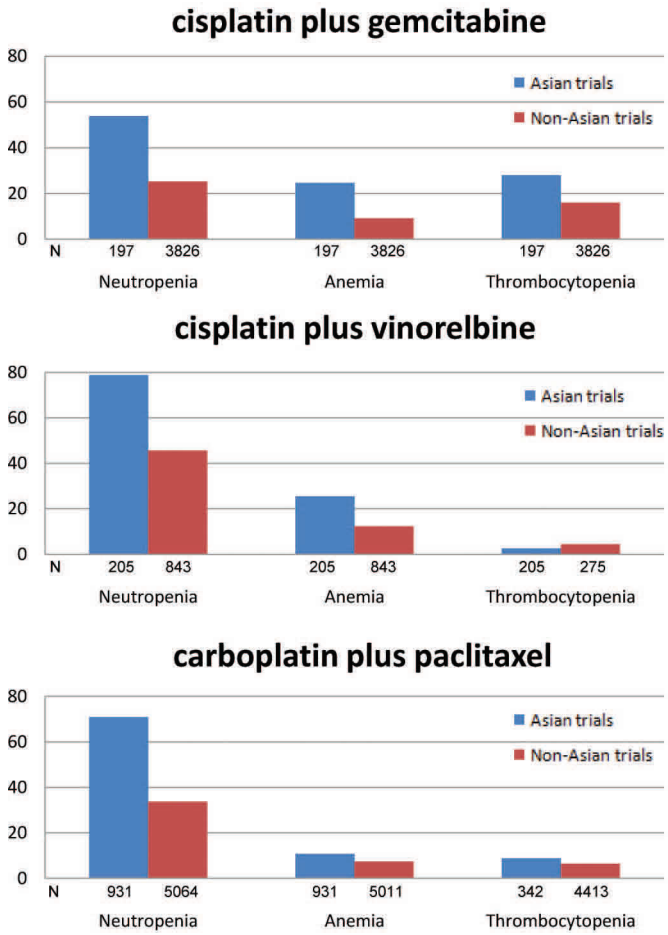
Study Selection

The flowchart for study selection is shown in Figure 2. We retrieved 328 articles on the regimen of CG, 216 articles on CV, and 361 articles on carboplatin and paclitaxel. Finally, we identified 12 phase II and 38 phase III trials of NSCLC with a total of 11,271 patients in three regimens.

All articles are listed in supplement 1 to 3B, Supplemental Digital Content 1 to 4; http://links.lww.com/JTO/A104, http://links.lww.com/JTO/A105, http://links.lww.com/JTO/A106, and http://links.lww.com/JTO/A108. In the regimen of CG, we identified four phase II trials and 14 phase III trials with a total of 4023 patients (supplement 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A104). Two trials were performed in Japan and China (Asian studies), and 16 trials were performed in the United States and Europe (non-Asian studies). In CV, one phase II trial and four phase III trials were identified with a total of 1253 patients (supplement 2, Supplemental Digital Content 1, http://links.lww.com/JTO/A105). Two trials were performed in Japan, and three trials were performed in the United States and Europe. In CP, we selected seven phase II trials and 20 phase III trials with a total of 5995 patients (supplement 3A, 3B, Supplemental Digital Content 3 and 4, http://links.lww.com/JTO/A106 and http://links.lww.com/JTO/A108). Three trials were performed in Asian countries including Japan, and 24 trials were performed in the United States and Europe. With regard to patient characteristics, median age from 56.4 to 66 years, and good performance status ratio (Eastern Cooperative Oncology Group 0 to 1, World Health Organization 0 to 1, or Karnofsky $\geq$70) accounted for 99.8% as a median. In the comparison of age between Asian trials and non-Asian trials, there was no significant difference in the three regimens; CG ($p = 0.64$), CV ($p = 0.50$), and CP ($p = 0.82$), respectively. In the performance status, there were more patients with poor performance status included in non-Asian study in the two regimens: CG ($p < 0.001$) and CV ($p < 0.001$); there was no significant difference in CP ($p = 0.45$).

Hematological Toxicity in Asian and Non-Asian Studies

As shown in Figure 3, grade 3/4 toxicities were more frequently observed in the Asian studies, when the actual number of all the patients was combined. Distribution of the frequency of grade 3/4 toxicity is shown in Figure 4. In a regimen of CG, neutropenia, anemia, and thrombocytopenia



CDDP GEM	N	Neutropenia	Anemia	Thrombocytopenia
Asian trials	197	53.9%	24.7%	28.0%
Non-Asian trials	3826	25.3%	9.2%	16.0%
χ2test OR (95% CI)		P<0.001 3.45 (2.58-4.61)	P<0.001 3.27 (2.30-4.56)	P<0.001 2.04 (1.48-2.82)

CDDP VNR	N	Neutropenia	Anemia	Thrombocytopenia
Asian trials	205	78.8%	25.6%	2.6%
Non-Asian trials	843	45.6%	12.4%	4.5% (N=275)
χ2test OR (95% CI)		P<0.001 4.43 (3.09-6.36)	P<0.001 2.43 (1.67-3.54)	P=0.323 0.57 (0.57-1.59)

CBDCA PTX	N	Neutropenia	Anemia	Thrombocytopenia
Asian trials	931	70.9%	10.8%	8.8% (N=342)
Non-Asian trials	5064	33.7%	7.4% (N=5011)	6.5% (N=4413)
χ2test OR (95% CI)		P<0.001 4.79 (4.11-5.59)	P<0.001 1.52 (1.20-1.91)	P=0.115 1.39 (0.94-2.06)

FIGURE 3. Comparison of grades 3 and 4 hematological toxicity between combined Asian and non-Asian trials.

were more frequently observed in Asian studies than in non-Asian studies with a statistical significance ($p < 0.001$). In a regimen of CV, neutropenia and anemia were also significantly more frequently observed in Asian studies ($p < 0.001$) except thrombocytopenia ($p = 0.323$). In a regimen of CP, neutropenia and anemia occurred more frequently in Asian studies ($p < 0.001$), again excepting thrombocytopenia ($p = 0.115$).

Hematological Toxicity in Sensitivity Analysis

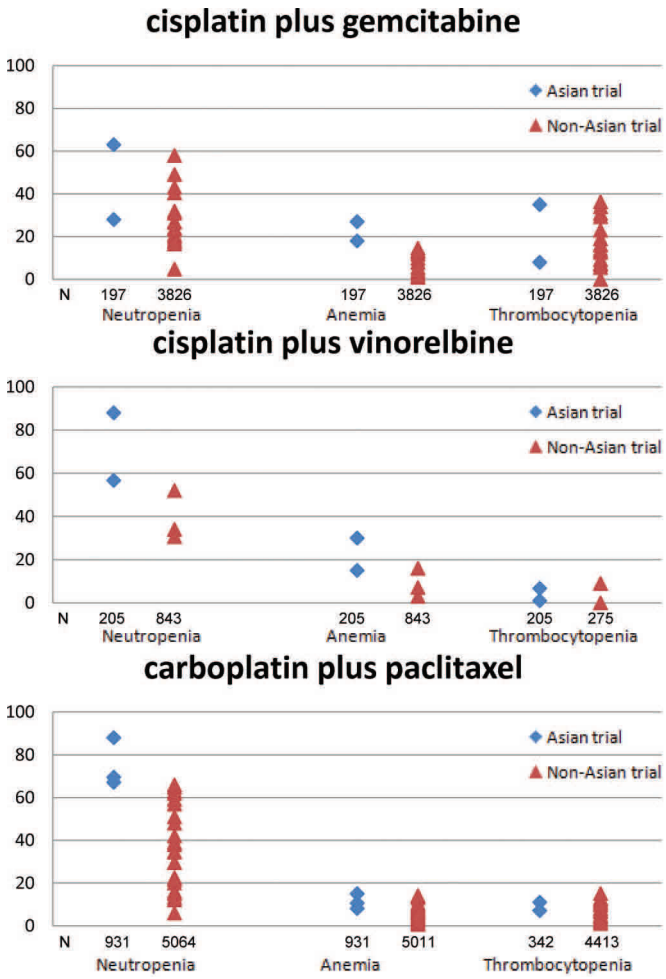
Asians in the Asian trial were Japanese and Chinese from East Asia, whereas non-Asians were large and heterogeneous populations without a specified origin. We extracted Asian and non-Asian patients from both separated Asian trials/non-Asian trials and trials enrolling Asian and non-Asian patients.

In a total of 50 trials of NSCLC that were identified, only 14 trials reported ethnic origins of the study participants. Among the 14 trials, 8 trials included Asian patients and they showed that the ratio of Asian and non-Asian patients is imbalanced, and the proportion of Asian patients ranged from 0.8 to 17.4% (median 6.0%).

We estimated the ratio of Asian patients in the 36 trials with unknown ethnic origins. We calculated the hazard ratio ± 95% confidence interval of hematological toxicity (Asian/non-Asian) in each regimen, varying a putative Asian population from 0 to 18%. We adopted the lowest frequency of each hematological toxicity observed in actual Asian trials, and we could reduce the margin of error to be more accurate, minimizing the possible differences in severity of hematological toxicities between Asians and non-Asians (Figure 1). On the basis of these assumptions, nine models were created as shown in Figure 5. *x* axis is the ratio of Asian, and *y* axis is the OR. We showed how an OR changed as we changed the Asian ratio. The green dotted line represents the OR of 1. As shown in Figure 5, even if we changed the Asian ratio, more frequent grade 3/4 neutropenia and anemia were observed significantly in Asian patients in the three regimens. However, there was no significant difference between Asian and non-Asian in frequency of severe thrombocytopenia.

Survival Analysis

We identified six phase II and 38 phase III trials of NSCLC in three regimens in survival analysis. We excluded the IRESSA Pan Asia Study trial because most of the patients in the study were never-smokers in East Asia who had outstanding



CDDP GEM	N	Neutropenia	Anemia	Thrombocytopenia
Asian trials	197	53.9% (28.0-63.0)	24.7% (18.0-27.0)	28.0% (8.0-35.0)
Non-Asian trials	3826	25.3% (4.8-58.0)	9.2% (1.0-14.6)	16.0% (0-36.3)

CDDP VNR	N	Neutropenia	Anemia	Thrombocytopenia
Asian trials	205	78.8% (56.7-88.0)	25.6% (15.0-30.0)	2.6% (1.0-6.7)
Non-Asian trials	843	45.6% (30.7-52.0)	12.4% (3.0-16.0)	4.5% (0-9.0) (N=275)

CBDCA PTX	N	Neutropenia	Anemia	Thrombocytopenia
Asian trials	931	70.9% (67.1-88.0)	10.8% (8.1-15.0)	8.8% (7.1-11.0) (N=342)
Non-Asian trials	5064	33.7% (5.9-66.0)	7.4% (0.6-14.1) (N=5011)	6.5% (1.0-15.1) (N=4413)

FIGURE 4. Comparison of grades 3 and 4 hematological toxicity between Asian and non-Asian trials; scatterplot.

good prognosis. In the comparison of overall survival by using Student's *t* test, median survival time was longer in the Asian studies than those in non-Asian studies as shown in Figure 6 (12.2 months versus 9.6 months, $p = 0.012$).

DISCUSSION

Global clinical trials including lung cancer have advanced year by year. Glickman et al.[9] reviewed 300 articles reporting the results of clinical trials in 1995–2005 and found that the number of countries serving as trial sites outside the United States more than doubled in 10 years, whereas the proportion of trials conducted in the United States and Western Europe decreased. Globalization of clinical trials may also shorten the timeline for clinical testing.

Although it is efficient to include patients globally for saving time and costs in completing large-scale clinical trials, ethnic difference in treatment benefit and toxicity is becoming a great concern. In IRESSA Survival Evaluation in Lung cancer study,[4] Asian patients lived longer compared with non-Asian patients treated with gefitinib (median 9.5 versus 5.2 months). EGFR mutation is a critical biomarker for EGFR-TKIs, and there is a higher rate of EGFR mutations in the Asian patients than whites, 19 to 61% versus 5 to 10%.[5] Ethnic difference in clinical benefit might be because of tumor biology among different ethnicities. However, instead of a large body of work focused on differences in clinical benefit, we find that those in hematological toxicity have not been fully studied. Given such a situation, we showed a significant difference of hematological toxicity due to cytotoxic chemotherapy between Asian and non-Asian in a pooled analysis on phase II and III clinical trials.

In this study, we showed that the degree of hematological toxicities of neutropenia and anemia was significantly different between Asian and the US/European studies. In sensitivity analysis, we demonstrated that Asian patients had a disadvantage in side effects compared with non-Asian patients who were mostly whites. Grade 3/4 neutropenia and anemia were more frequently observed in Asians in the common chemotherapy regimens of platinum doublets widely used in patients with NSCLC. Serious thrombocytopenia was also observed in CG, but not in CV and CP. It is suggested that dose setting be carefully conducted in global clinical trial and that dose modification according to ethnicity be considered.

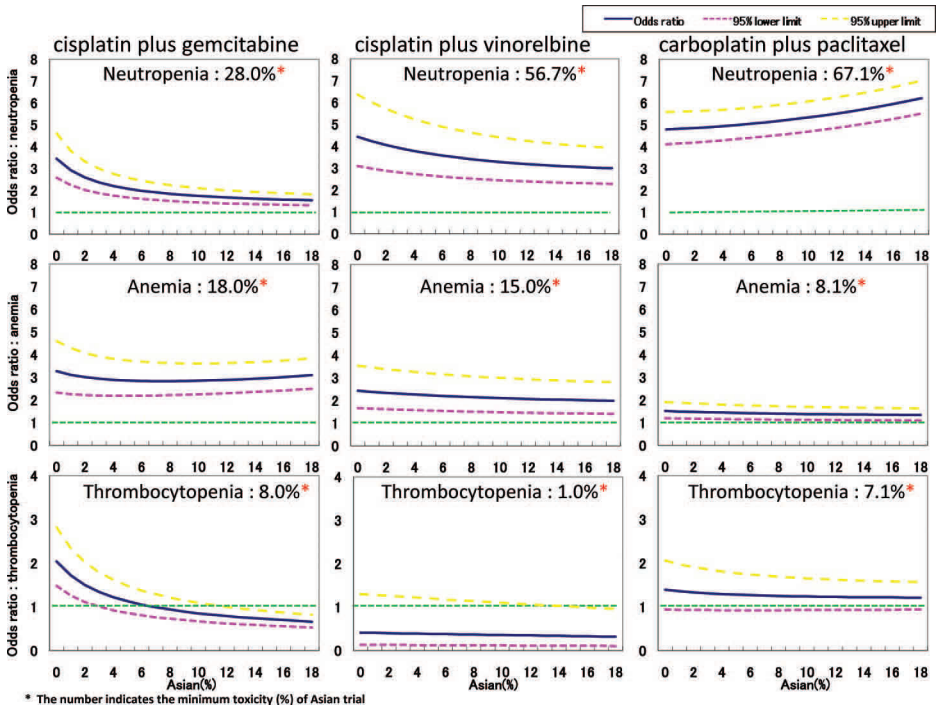


FIGURE 5. Sensitivity analysis: green dotted line represents the OR of 1. Red and yellow dotted lines represent probability with 95% confidence. Yellow dotted line is the highest probability. Red dotted line is the lowest probability. A difference is found when using the high figure in Figure 3. Because this is not representative of the entire group, it does not show a difference among all cases. If we use the lowest number, we reduce the margin of error to be more accurate. In this study, severe neutropenia and anemia were more frequently observed in Asians, excepting severe thrombocytopenia.

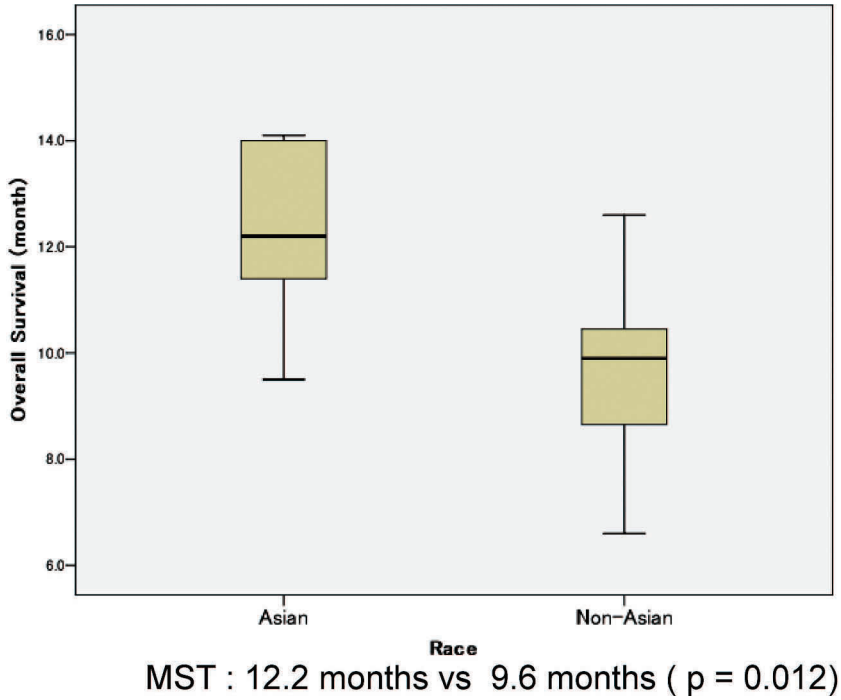


FIGURE 6. Survival and race: the comparison of overall survival time by using Student's *t* test.

There is substantial interindividual variability in drug metabolism.[10] Recent evidence suggests that there is even greater variability between individuals of different ethnicity. A number of genetic polymorphisms that reflect ethnic differences have been reported to affect pharmacokinetics and pharmacodynamics.[5] It is well known that pharmacokinetic factors that determine an individual's exposure to drugs and metabolites affect the potential for beneficial and toxic responses to that medicine, e.g., *CDA*3* for gemcitabine,[11] *ABCB1* for vinorelbine,[12] *CYP2C8* for paclitaxel,[13,14] and ERCC2, XPD for platinum compounds.[2,15]

Another explanation for ethnic difference is frequency of never-smokers in patients with NSCLC between Asians and whites. Epidemiological study showed that approximately 30% of patients with NSCLC were never-smokers in Asians, while 7 to 8% in whites.[16] In smokers, the dose-

normalized area under the plasma concentration–time curve of irinotecan was significantly lower compared with nonsmokers, and smokers experienced considerably less hematologic toxicity.[17] In addition, there was a significantly higher incidence of grades 3 and 4 neutropenia among patients treated with gemcitabine monotherapy without a history of smoking than among those with a history of smoking.[18] Therefore, smoking status may affect drug metabolism and toxicity, although this is still controversial.

Neutropenia during chemotherapy has been reported to be a predictor of longer survival in several studies.[19,20] In fact, among clinical trials analyzed in this study, we detected weak correlation between response rates and grade 3 and 4 hematological toxicities for neutropenia (data not shown). We showed that median survival time was better in the Asian studies than those in the non-Asian studies, although it is a statistical disadvantage without considering size of the study. Side effects of neutropenia shown in this study may affect the prognosis of Asians as well. In the international First-Line ErbituX in lung cancer study,[21] the 11% of patients who were Asian had a considerably better overall prognosis regardless of study treatment compared with whites (median survival, 19.5 months versus 9.6 months). Again, EGFR mutations were frequently observed in Asians, and survival benefit for Asians seemed to be because of EGFR mutations and EGFR-TKI treatment. Recently, Gandara et al.[22] reported that tumors with EGFR-activating mutations have lower expression level of genes associated with DNA repair, such as ERCC1 and suggested that low DNA repair capacity may be a more direct explanation for improved efficacy of platinum-based chemotherapy in Asian populations.

There are some limitations in our study. First, our unique methods may potentially influence publication bias. However, our primary focus of toxicity is not associated with end point originally designed in each clinical trial, and our results cannot be affected by published data selected. Other confounding factors that influence hematological toxicity also should be considered. There was no significant difference in age distribution between Asian trial and non-Asian trial, and there were poorer performance status patients included in non-Asian study, which likely relates with more side effects. More side effects occurred in Asian trials, which included more good performance status patients, and unbalanced performance status distribution between the two study groups cannot minimize our results. Second, the number of Asian trials was relatively small, and the chemotherapy regimen of cisplatin and pemetrexed was not included in this study, which is also commonly used globally. However, no phase II or phase III studies on cisplatin and pemetrexed conducted in Asian countries have been reported to date. Global clinical trials have increased, and more Asians will be enrolled in the near future. Third, the data of each trial were not based on individual data, and side effects are also affected by frequency of examination of blood count. In addition, each study has its own follow-up algorithm. There may be an argument that Asian doctors conducted the test more, which leads to more severe toxicity appearing in Asian study. However, SWOG and Japan Multi-National Organization common arm analysis used an identical protocol and they showed significant difference between them, and grades 3 and 4 neutropenia and febrile neutropenia were significantly greater than in SWOG trial.[2] This common arm analysis is a promising and reliable method to investigate toxicity and genetic backgrounds particularly for the study of ethnic differences. Another approach can be inclusion of the information of ethnicity in designing clinical trials, which will be collected individually for future meta-analysis.

In conclusion, we demonstrated that severe hematological toxicities were more frequently observed in Asian patients compared with non-Asians who were mainly white. This study suggests that global clinical trials should be carefully designed and conducted to account for potential genetic differences in the patient. Large-scale prospective studies focused on ethnic differences are warranted for global public benefit.

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